



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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BETHESDA, MARYLAND 20014

Enclosure

Building 2, Room B2-08

January 25, 1974

Dr. A. Mirsky
Rockefeller University
New York, New York 10021

Dear Dr. Mirsky:

I apologize once again for the delay in writing to you. As you may know through Mrs. Sternfeld of the Rockefeller Library I visited there on October 29 during your absence. I have since had no opportunity to visit New York, and to avoid further delay I am currently making revisions to the paper.

I enclose a revised page and footnotes relating to your own involvement. I hope they meet your objections as expressed in your letter of 6/29/73. Please remember that I have no personal involvement in this matter, that I do not claim to be infallible and that I seek a balanced view. Also please bear in mind that this was not the main area covered by the paper (as emphasized in ref. 144b).

This does not mean, however, that we have no further interest in the topic. I still very much want to interview you for the record and for future work when I next have an opportunity to visit New York.

Yours sincerely,

Jack Cohen
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historiographical formulae they do tend to ignore the unique aspects of situations to which they are meant to apply in favor of their supposed similarities. In doing so they do not tell us why a particular discovery was "premature". Thus, in the case of Avery et al.'s work on the transformation by DNA it is useful to know that a war was still in progress, that Avery was an old man (67) at the time this work was published and that he had a reserved temperament (139). Several people opposed Avery's modest conclusions in the light of their own beliefs in the genetic primacy of proteins (143). Also, unfortunately, experimental follow-up by Avery's associates to answer objections to the work were largely unpublicized (143b). These and other factors presumably contributed to the delay of eight years, until the publication of confirmatory results by Hershey and Chase in 1952 (144), before the supposed general acceptance of the fact that DNA was the transforming principle (141). Nevertheless, many people were active in this intervening period (144b) and several people did in fact accept the implications of the results of Avery et al. (145), including Erwin Chargaff who was motivated to begin his own significant work on DNA as described above. For such people Avery et al.'s work could hardly be described as "premature". Furthermore, the nucleic acid component of nuclein was considered to have a possibly important role in heredity long before Avery's work. Thus, E. B. Wilson in the second edition of his influential book "The Cell", published in 1900 stated:

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Revised footnote 143.

Alfred Mirsky, also working at the Rockefeller Institute, has been mentioned as one of the chief questioners of DNA as the transforming substance by Chargaff (ref. 75), Hotchkiss (ref. 139) and Stent (Molecular Genetics, Freeman, San Francisco, 1971, p. 180). For example in "The Chemical Composition of Isolated Chromosomes" (J.Gen.Physiol., 31, 7-18 (1947)), Alfred Mirsky and Hans Ris state

"The form of the chromosome is due primarily to the protein thread of the residual chromosome...the residual chromosome (is) the basis for the linear order of the genes."

On the other hand, Mirsky's views at the time are most clearly expressed as;

Avery and his colleagues have shown decisively by inactivation experiments that desoxyribose nucleic acid is an essential part of the transforming agent, and if there actually is no protein in their preparation, it would be obvious that the agent consists of nothing but nucleic acid. This is a conclusion of the greatest interest in the study of the chemical basis of biological specificity, and it should therefore be scrutinized carefully. There can be little doubt in the mind of anyone who has prepared nucleic acid that traces of protein probably remain in even the best preparations. With the tests now available for detecting how much protein is present in a nucleic acid preparation, it is probable that as much as 1 or 2 per cent of protein could be present in a preparation of "pure, protein-free" nucleic acid. One of the most sensitive direct tests for protein is the Millon reaction,

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but in our experience a nucleic acid preparation containing as much as 5 per cent of protein would give a negative Millon test. At present the best criterion for the purity of a nucleic acid preparation is its elementary composition and especially the nitrogen:phosphorus ratio. Presence of 2 per cent of protein would increase this ratio, but only by an amount that is well within the range of variation found for the purest nucleic acid preparations. No experiment has yet been done which permits one to decide whether this much protein actually is present in the purified transforming agent and, if so, whether it is essential for its activity; in other words, it is not yet known which the transforming agent is--a nucleic acid or a nucleoprotein. To claim more, would be going beyond the experimental evidence.

(A. E. Mirsky and A. W. Pollister, "Chromosomin, A Deoxyribose Nucleo-protein Complex of the Cell Nucleus", J.Gen.Physiol., 30, 1946, p. 134-135). Dr. Mirsky has stated his attitude as follows; "From the beginning I considered DNA as an essential part of the transforming principle, and after it was proven by Hotchkiss that there was practically no protein present I accepted the conclusion without reservations" (letter dated 6/29/73).

Ref. footnote 143b.

For example, Maclyn McCarty and O. T. Avery, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types. II. Effect of Deoxyribonuclease on the Biological Activity of the Transforming Substance", J.Experimental.Med., 83, 89-96 (1946). In the summary they state

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"It has been shown that extremely minute amounts of purified preparations of desoxyribonuclease are capable of bringing about the complete and irreversible inactivation of the transforming substance of Pneumococcus Type III". McCarty has said "The discussion of the results reported in this was directed specifically toward some of the objections.... I will admit that this paper is cited infrequently and usually not mentioned at all in any discussion of the 1944 paper" (letter dated 7/10/73). Also, for example, Rollin D. Hotchkiss "Etudes sur le facteur transformant du pneumocoque", Colloq. Int. Centre Natl. Recherche Scie. (Paris), 8, 57-65 (1949).

Ref. 144b.

A detailed analysis of the work on transformation and DNA in the period 1944-1952 is beyond the scope of the current work. However, among those active in this field, apart from McCarty and Hotchkiss, were Austrian, Ephrussi-Taylor, Zamenhof and Seymour Cohen (the latter two from Chargaff's laboratory). Hotchkiss has described this work from his own vantage point ("Gene, Transforming Principle, and DNA", Phage and the Origins of Molecular Biology (ed. J. Cairns, G. S. Stent, and J. D. Watson) Cold Spring Harbor Laboratories, 1966, p. 180-200) and has emphasised that one factor in the apparent delay in the assimilation of Avery et al.'s work was the difficulty in following it up experimentally (letter dated 7/19/73).